TRANSLATION

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference XII 875-05	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/DE2004/002760	International filing date *(day/month/year)* 13.12.2004	Priority date *(day/month/year)* 12.12.2003
International Patent Classification (IPC) or national classification and IPC A61K31/401, A61K31/506, A61P35/00		
Applicant SALAMA, Zoser, B.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:

      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DE2004/002760

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1-27 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

nos. 1-28 as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* _____ received by this Authority on _____

nos.* _____ received by this Authority on _____

☐ the drawings:

sheets _____ as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DE2004/002760

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 9,11,12,18,20 (in part),9-28

because:

☒ the said international application, or the said claims Nos. 9-28
relate to the following subject matter which does not require an international preliminary examination (*specify*):

See Supplemental Box

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 9,11,12,18,20(in part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DE2004/002760

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-28	YES
	Claims		NO
Inventive step (IS)	Claims	1-28	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-8	YES
	Claims	9-28 (See Supplemental Box)	NO

2. Citations and explanations (Rule 70.7)

1. This international preliminary report on patentability makes reference to the following documents cited in the search report:

D1: US-A-6 066 665 (HOERRMANN ET AL), 23 May 2000 (2000-05-23)

D2: US-A-6 153 643 (HOERRMANN ET AL), 28 November 2000 (2000-11-28)

D3: WICHA M S ET AL: "BLOCKING BASEMENT MEMBRANE COLLAGEN DEPOSITION INHIBITS THE GROWTH OF 7 12 DI METHYL BENZANTHRACENE INDUCED RAT MAMMARY TUMORS", CANCER LETTERS, Vol. 12, No. 1-2, 1981, pages 9-22, XP008047843, ISSN: 0304-3835

D4: EP-A-1 258 248 (TAP PHARMACEUTICAL PRODUCTS, INC), 20 November 2002 (2002-11-20)

D5: WO 01/34134 A (ELI LILLY AND COMPANY; SAWYER, JASON, SCOTT; TEICHER, BEVERLY, ANN; BE), 17 May 2001 (2001-05-17)

D6: WO 01/34198 A (ELI LILLY AND COMPANY; SAWYER, JASON, SCOTT; TEICHER, BEVERLY, ANN; BE), 17 May 2001 (2001-05-17)

D7: BUCK TODD B ET AL: "cis-hydroxyproline stimulates the growth of rat mammary carcinoma cells", IN

VIVO (ATTIKI), Vol. 14, No. 1, January 2000 (2000-01), pages 7-12, XP008047847

2. The applicant should note that the international preliminary examination report relates only to aspects with respect of which the international search report was established (in this case, CHP with gemcitabine for the treatment of tumours).

3. In the PCT Contracting States, there are no uniform criteria for assessing the industrial applicability of claims 9-28 in their present form. Patentability can also depend on the wording of the claims. The EPO, for example, does not recognise the industrial applicability of claims to the use of a compound in a medical treatment; it does, however, allow claims to the first use of a known compound in a medical treatment or to the use of such a compound in the manufacture of a drug for a new medical treatment.

Novelty

3. The present application meets the requirements of PCT Article 33(1) because the subject matter of claims 1-28 is novel (PCT Article 33(2)). No document discloses a combination agent comprising cis-hydroxy-proline and gemcitabine, or its use for the treatment of cancer.

Inventive step

4.1 The subject matter of claims 1-28 appears to meet the requirements of PCT Article 33(3), i.e. to involve an inventive step.

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

D1-D3 disclose the use of cis-hydroxy-proline (CHP) (as well as N-methyl-cis-hydroxy-proline, in the case of D1) for the treatment of cancer.

D4-D6 disclose the use of gemcitabine, alone or together with other antitumoral agents, for the treatment of cancer.

The subject matter of claims 1-28 differs from D1-D6 in that both compounds are administered together. The present invention can therefore be considered to address the problem, starting from the citations D1-D6, of providing an alternative treatment for the above-mentioned diseases.

It would not be obvious for a person skilled in the art to use two or more known anti-tumoral compounds, in combination, for the treatment of cancer: the use of a combination of two or more active substances having the same, already known effect should be considered inventive if it is proved to have surprising effects. Synergy can serve as proof of inventive step. The applicant shows that the compound CHP did not cause any tumour weight or metastasis reduction in rats and that gemcitabine induced an effect, causing tumours to lose about 7% of their weight, while the administration with the combination agent according to the invention reduced tumour diameter by more than 55%. Synergy has therefore been proved. Moreover, the claimed combination therapy has been shown to achieve a good therapeutic success in the treatment of tumours of colorectal adenocarcinoma patients, since the

presence of CHP permitted gemcitabine to be administered in smaller doses and with shorter treatment cycles.

4.2 Moreover, document D7, which is cited in the search report, discloses that the compound CHP causes mammal cancer cells to grow. This knowledge would lead a person skilled in the art to expect CHP to show an activity together with other compounds.

4.3 In response to the objection under PCT Article 33(3) that the subject matter of the main claim includes non-inventive compositions and hence does not meet the requirements of PCT Article 33(3), the applicant has proved that the combination of cis-hydroxy-proline (CHP) and gemcitabine convincingly represents a solution to the problem, i.e. has a synergistic effect (see point 4.1).

4.4 The subject matter of claims 1-28 is therefore inventive (PCT Article 33(3)).

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

BOX III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 9, 11, 12, 18 and 20 to a second medical indication are not admissible under PCT Articles 5 and 6. The therapeutic use is functionally defined in terms of an action mechanism ("diseases associated with cell growth, cell differentiation and/or cell division", "tumour growth, tumour propagation, tumour angiogenesis, tumour invasion, tumour infiltration and/or tumour metastasis", "monitoring of the effectiveness of an anti-tumour treatment"), this functional definition failing to involve a practical application in the form of a defined, actual treatment of a pathological disturbance (disease).

This objection could be eliminated either by inclusion in the claims of a list of the pathological disturbances (diseases: tumours, in this case) mentioned in the application, or by a demonstration that auxiliary means exist for helping a person skilled in the art to judge what further disturbances are covered by the functional definition.

In the present case, the claims lack the corresponding support and the application lacks the requisite disclosure. No international preliminary examination report is established for aspects of the invention which are not the subject of the search report.

Supplemental Box

2. Claims 9-28 relate to subject matter which, in the opinion of this Authority, falls under PCT Rule 67.1(iv).

Claims 18 and 20 relate to subject matter which, in the opinion of this Authority, falls under PCT Rule 67.1(iv), even after they have been reworded into claims to a "use of…for producing a medicament for the treatment of…".

Following the progression of a disease by "monitoring the effectiveness of a medicament" is part of the typical activities and duties of a doctor exercising his healing science. These are typical non-commercial, non-industrial activities in the field of human medicine, which PCT Rule 67.1(iv) is intended to keep free from patent law restrictions.

A doctor is always able to prescribe an efficient mode of administration and to monitor the effectiveness of a therapy, in order to treat all patients according to their individual needs.

It is questionable that the feature in question could actually be regarded as a further medical indication.

Consequently, no opinion is formed on the industrial applicability of the subject matter of these claims (PCT Article 34(4)(a)(i)).